# 4-Bromo-1-(3-[$^{18}$F]fluoropropyl)-2-nitroimidazole
# 4-Br[$^{18}$F]FPN

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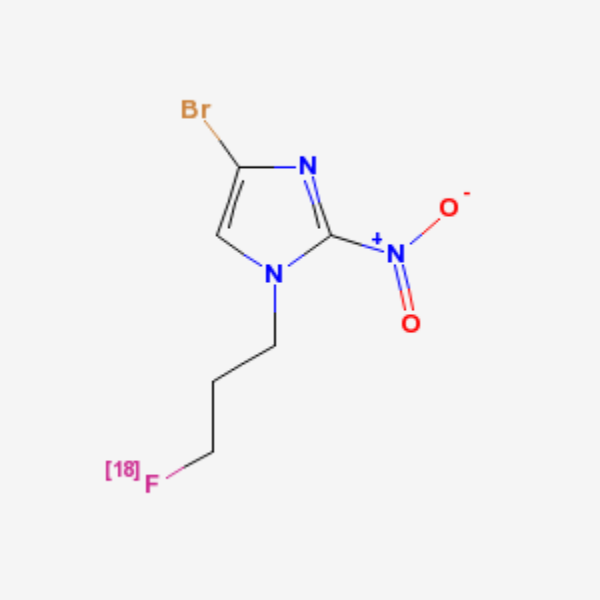
**Chemical name:** 4-Bromo-1-(3-[$^{18}$F]fluoropropyl)-2-nitroimidazole
**Abbreviated name:** 4-Br[$^{18}$F]FPN; 4-BrFPN
**Synonym:**
**Backbone:** Compound
**Target:** Hypoxic cells (brain)
**Mechanism:** Intracellular reduction and binding
**Method of detection:** PET
**Source of signal:** $^{18}$F
**Activation:** No
***In vitro* studies:** Yes
**Rodent studies:** Yes
**Other non-primate mammal studies:** No
**Non-human primate studies:** No
**Human studies:** No

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## Background

[PubMed]

Hypoxia in malignant tumors is thought to be a major factor limiting the efficacy of chemotherapy and radiotherapy, and its accurate diagnosis is considered a very important and urgent problem to address. This has led to the search and development of hypoxia-targeted imaging techniques and non-invasive markers of tumor hypoxia. Among those, $^{18}$F-labeled nitroimidazoles, used in conjunction with positron emission tomography (PET), offer an alternative that is less invasive and less prone to sampling error than the Eppendorf (oxygen) electrode method (1, 2).

Initial development of nitroimidazoles for *in vivo* imaging used radiohalogenated derivatives of misonidazole such as fluoromisonidazole ([$^{18}$F]FMISO [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=micad.chapter.FMISO]), which was introduced in 1984 and has now become the most widely

used nitroimidazole derivative used with PET. Novel 2-nitroimidazoles, such as [$^{18}$F]FETA (3), [$^{18}$F]FETNIM (4), [$^{18}$F]FPN (5), and 4-Br[$^{18}$F]FPN (6), are also currently under investigation as PET markers for hypoxia.

4-Br[$^{18}$F]FPN was designed to improve the electron affinity of the 2-nitroimidazole ring, when compared with [$^{18}$F]FPN. Indeed, on the basis of molecular orbital calculations, the introduction of a bromine atom at the 4-position in the nitro-bearing ring seems to significantly lower the orbital energy of the lowest unoccupied molecular orbital ($E_{LUMO}$), which may facilitate metabolic reduction and trapping under hypoxia. Studies of 4-Br[$^{18}$F]FPN in rats and mice show enhanced tumor-to-blood and tumor-to-muscle ratios compared with [$^{18}$F]FPN (see details in the Rodents section), but both 4-Br[$^{18}$F]FPN and [$^{18}$F]FPN show a tumor localization less favorable than [$^{18}$F]FMISO.

The oxygen-dependent metabolism of nitroimidazoles is an intracellular process consisting of a series of one-electron reductions. The nitro-radical anion produced in the first reduction step is very reactive toward oxygen, leaving no substrate for the second step of the reduction process. In contrast, an environment of low oxygen concentration induces further reductive reactions that ultimately lead to the formation of either reactive products that are able to covalently bind to cell components or charged species that diffuse slowly out of the tissues (7). The reactive products observed during this multi-step process include nitroso (2e-), hydroxylamine (4e-), and amine (6e-) derivatives. When the fragmentation of the imidazole ring occurs, reactive portions of the molecule, such as glyoxal, bind to macromolecular components of cells in tissues and tumors (2).

## Synthesis

[PubMed]

4-Br[$^{18}$F]FPN can be synthesized by a [$^{18}$F]fluoride ion displacement reaction of the tosylate precursor, as reported by Yamamoto et al. (6). In this method, the tosylate is prepared by coupling di-tosyl propylate with 2-nitroimidazole in the presence of triethylamine *N,N*-dimethylformamide (5). The direct bromination of the tosylate with an excess of $Br_2$ in dioxane produces 4-bromo tosylate. 4-BrFPN is obtained by fluoride substitution on the tosylate precursor using tetrabutylammonium fluoride (71% yield).

The radiosynthesis protocol described by Yamamoto et al. (6) leads to a radiochemical yield of about 33% and a radiochemical purity >96% for 4-Br[$^{18}$F]FPN. The total reaction time (including purification) is 40 min. The optimal conditions are obtained with a 15-min reaction time at 80°C in acetonitrile.

## *In Vitro* Studies: Testing in Cells and Tissues

[PubMed]

*In vitro* studies using Chinese hamster V79 cells were performed to assess the radiosensitizing effectiveness of 4-Br[$^{18}$F]FPN on hypoxic cells, as published previously (6). Experiments were conducted in Minimal Essential Medium containing 1% dimethylsulfoxide. The sensitizer enhancement ratio (SER) for 4-Br[$^{18}$F]FPN was calculated as the ratio of the radiation dose required to obtain a

survival rate of the cells of 50% in the absence of 4-Br[$^{18}$F]FPN to the radiation dose required in the presence of 4-Br[$^{18}$F]FPN (for a similar survival rate). The SER for 4-Br[$^{18}$F]FPN was 1.65 for a 1 mM concentration, which is not significantly different from those obtained for [$^{18}$F]FMISO (1.60) and [$^{18}$F]FPN (1.81) (5).

# Animal Studies

## Rodents

[PubMed]

The biodistribution of 4-Br[$^{18}$F]FPN was assessed *in vivo* using normal Wistar rats and C3H mice bearing methylcholanthrene-induced fibrosarcoma tumors at 5, 15, 30, and 60 min after intravenous injection (6).

In normal rats, a fast transport of the radiotracer to tissues was observed, and the extent of defluorination for 4-Br[$^{18}$F]FPN (measured by bone radioactivity) was low during the first 30 min (and increased slightly thereafter). The highest uptakes were in the liver and kidney (13.43 ± 1.73% and 8.00 ± 0.94% dose/g, respectively, at 30 min after injection). The tumor-to-blood ratio at 30 min after injection was 0.777 ± 0.053% dose/g. Brain uptake was rapid, and its maximum (0.41 ± 0.15% dose/g) occurred at <5 min after injection. A rapid washout from the normal brain, with no observed accumulation, was also observed, making 4-Br[$^{18}$F]FPN a potential candidate for PET imaging of brain hypoxic tissue.

In the studies of mice, the tumors did not seem to significantly influence the uptake of 4-Br[$^{18}$F]FPN in normal tissues, and tumors showed a significant retention of the tracer. The concentrations of radioactivity in the tumor mass obtained at 30 and 60 min were 2.4% and 2.1% dose/g, respectively. Those values were found to be higher than those reported for [$^{18}$F]FPN at 30 and 60 min after injection (1.5% and 1.6% dose/g, respectively) using the same rodent tumor model (5). Tumor-to-blood and tumor-to-muscle ratios were 1.19 and 2.05 at 60 min after injection (compared with 0.79 and 1.38 for [$^{18}$F]FPN (5)). A radio-TLC analysis of accumulated radioactivity in tumor and muscle at 60 min after injection showed the formation of polar metabolites, which may indicate the presence of bioreductive metabolism and binding within the tumor.

In summary, the research literature indicates that 4-Br[$^{18}$F]FPN offers more favorable tumor-to-blood and tumor-to-blood ratios, compared with the non-bromide analogs of [$^{18}$F]FPN. Nevertheless, 4-Br[$^{18}$F]FPN has a lower tumor localization than [$^{18}$F]FMISO, although their tumor-to-background ratios do not differ substantially at 30-60 min after injection (6). Therefore, lowering the $E_{LUMO}$ of a molecule appears to be insufficient to improve the biodistribution properties and/or to enhance hypoxic selectivity.

## Other Non-Primate Mammals

[PubMed]

No publication is currently available.

## Non-Human Primates

[PubMed]

No publication is currently available.

# Human Studies

[PubMed]

No publication is currently available.

# References


1. Nunn A, Linder K, Strauss HW. Nitroimidazoles and imaging hypoxia. Eur J Nucl Med 22(3):265–280; 1995. (PubMed)
2. Hodgkiss RJ. Use of 2-nitroimidazoles as bioreductive markers for tumour hypoxia. Anticancer Drug Des 13(6):687–702; 1998. (PubMed)
3. Rasey JS, Hofstrand PD, Chin LK, Tewson TJ. Characterization of [18F]fluoroetanidazole, a new radiopharmaceutical for detecting tumor hypoxia. J Nucl Med 40(6):1072–1079; 1999. (PubMed)
4. Yang DJ, Wallace S, Cherif A, Li C, Gretzer MB, Kim EE, Podoloff DA. Development of F-18-labeled fluoroerythronitroimidazole as a PET agent for imaging tumor hypoxia. Radiology 194(3):795–800; 1995. (PubMed)
5. Yamamoto F, Oka H, Antoku S, Ichiya Y, Masuda K, Maeda M. Synthesis and characterization of lipophilic 1-[18F]fluoroalkyl-2-nitroimidazoles for imaging hypoxia. Biol Pharm Bull 22(6):590–597; 1999. (PubMed)
6. Yamamoto F, Aoki M, Furusawa Y, Ando K, Kuwabara Y, Masuda K, Sasaki S, Maeda M. Synthesis and evaluation of 4-bromo-1-(3-[18F]fluoropropyl)-2-nitroimidazole with a low energy LUMO orbital designed as brain hypoxia-targeting imaging agent. Biol Pharm Bull 25(5):616–621; 2002. (PubMed)
7. Bruehlmeier M, Roelcke U, Schubiger PA, Ametamey SM. Assessment of hypoxia and perfusion in human brain tumors using PET with 18F-fluoromisonidazole and 15O-H2O. J Nucl Med 45(11):1851–1859; 2004. (PubMed)